T cell dynamics in slow infection

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How do vaccines work?

The race between infection and immunity.

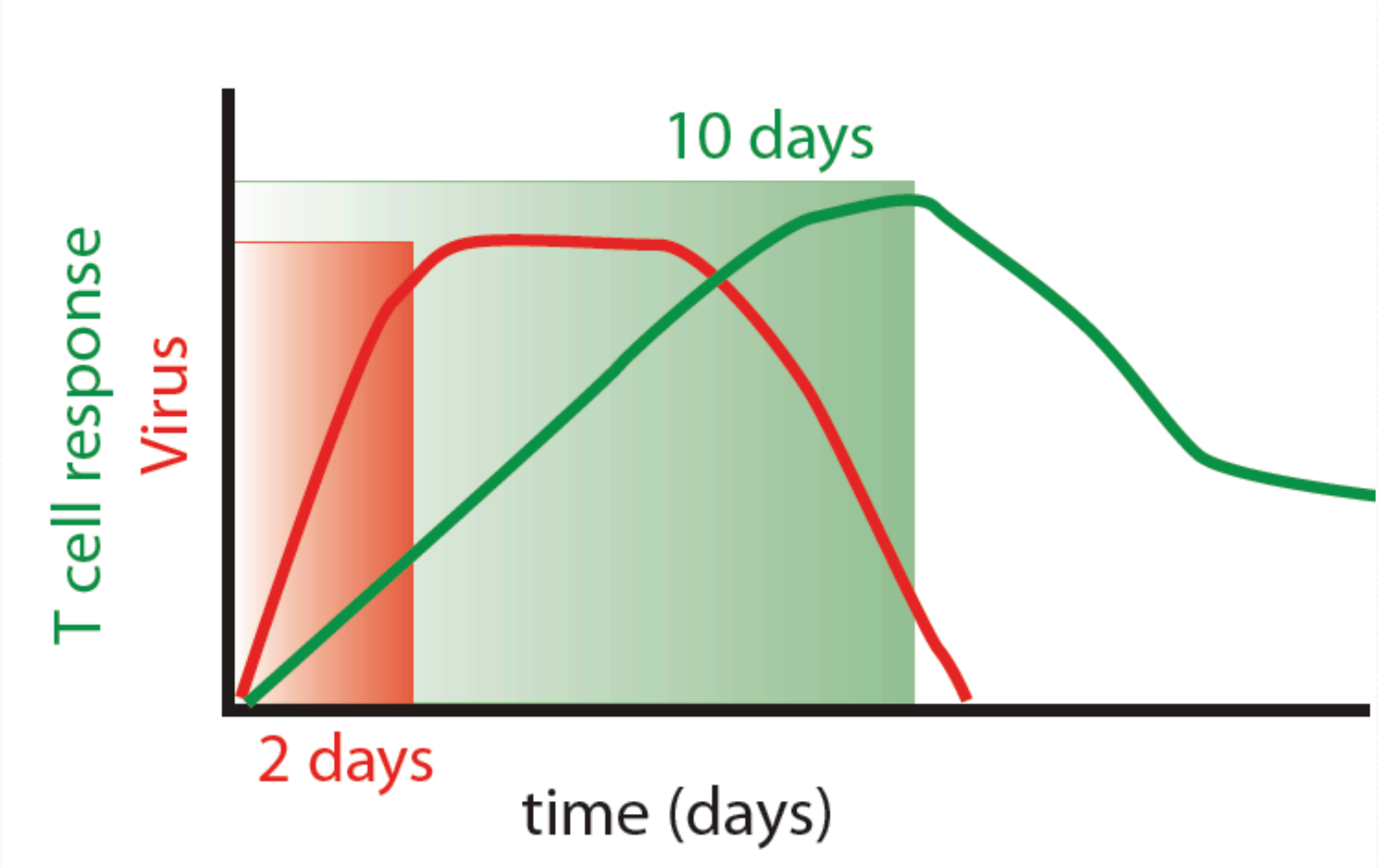
Davenport, Trends in Immunology 2009.

The race between infection and immunity.

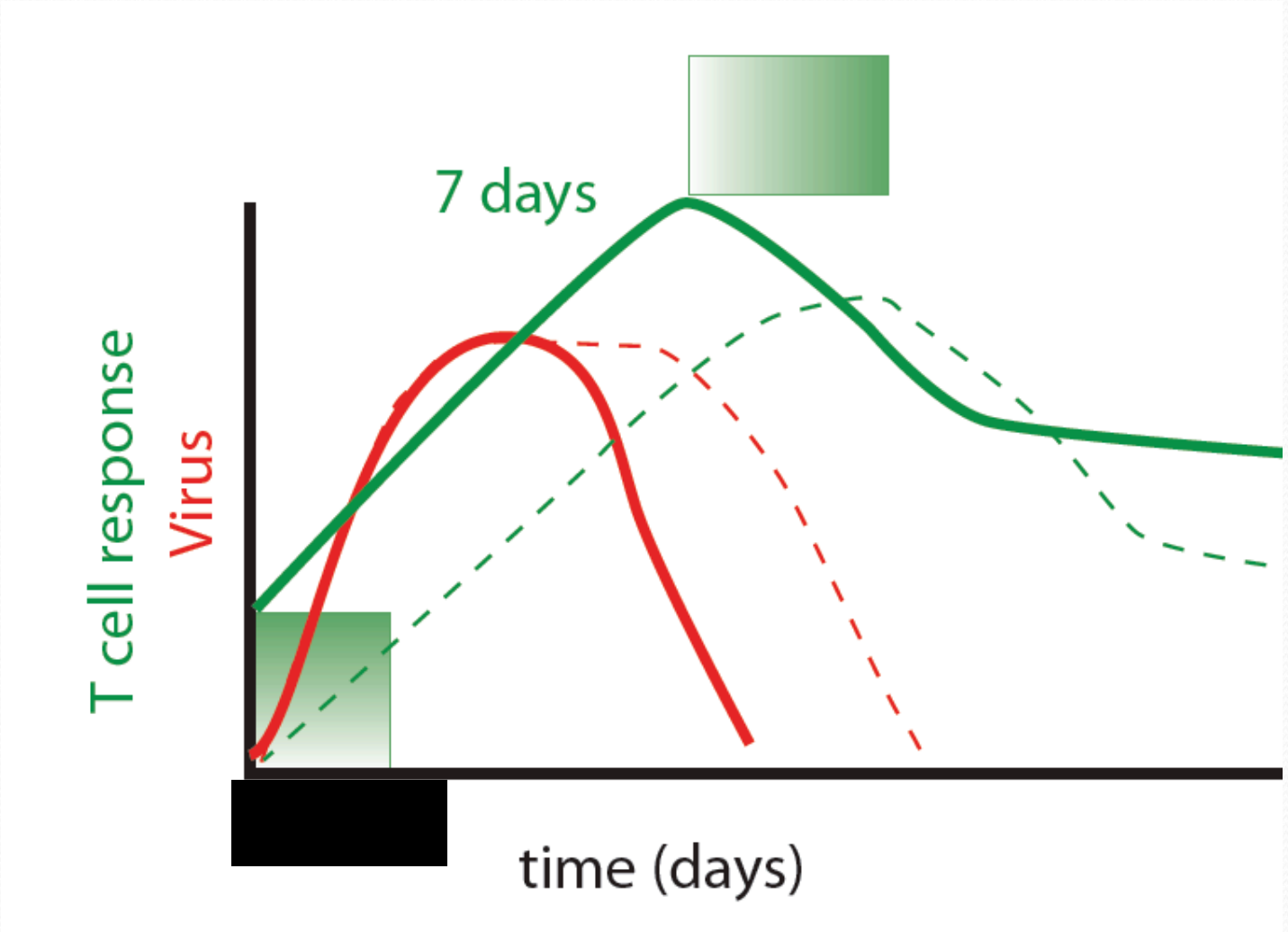
- Infectious agents can grow extremely rapidly (doubling every hour).
- Adaptive immune response divides slowly by comparison (4-6 hours)


1
2
3
4
5
6

The race between infection and immunity.



“Headstart” of vaccination.



Implications of “race” paradigm

- Slowly growing pathogens should be more easily controlled.

- Pathogens that grow more slowly than lymphocytes (doubling time >4-6 hours) should be rapidly overcome.

Davenport, Trends in Immunology 2009.

Implication of “race” paradigm

- Slowly growing pathogens should be more easily controlled.
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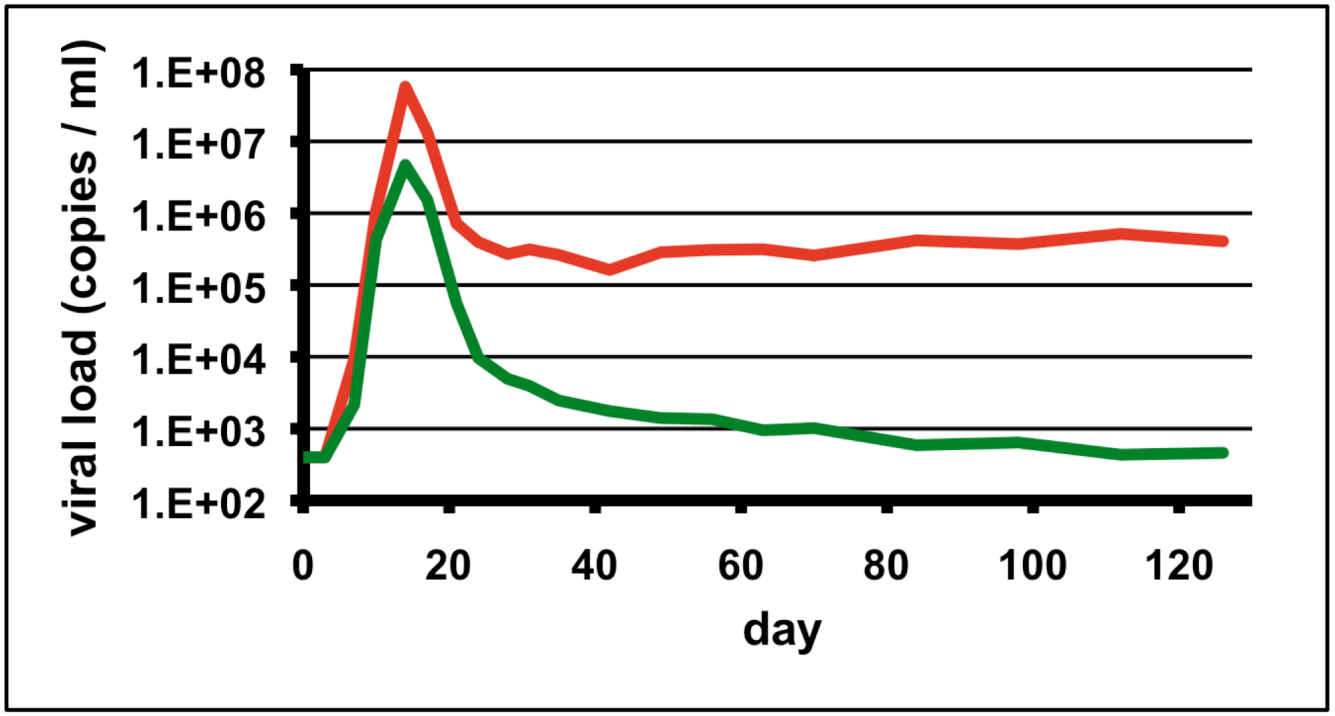
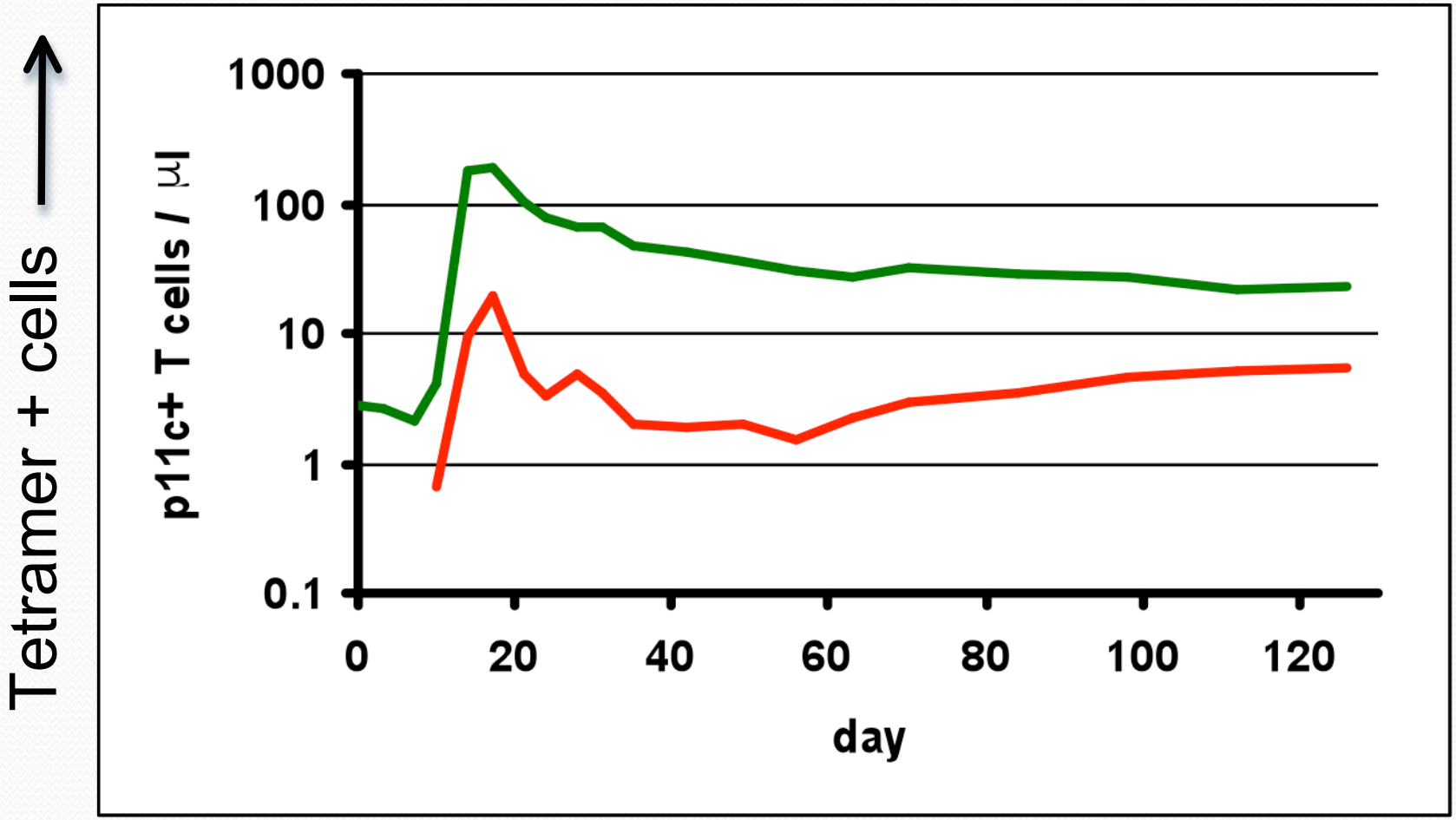
Slow pathogens: - establish chronic infection
- are resistant to vaccination.

Slow viral growth in SHIV
doubling time of virus = 12 h



Davenport *et al*, *Journal of Virology* 78, p10096 (2004)

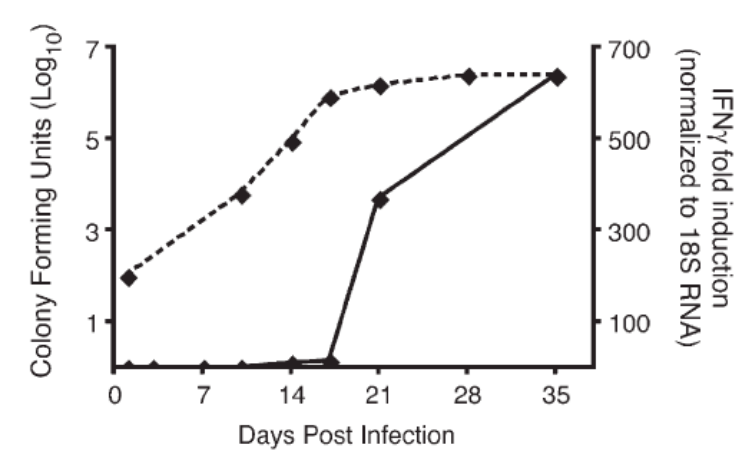
Delayed & slow T cell growth



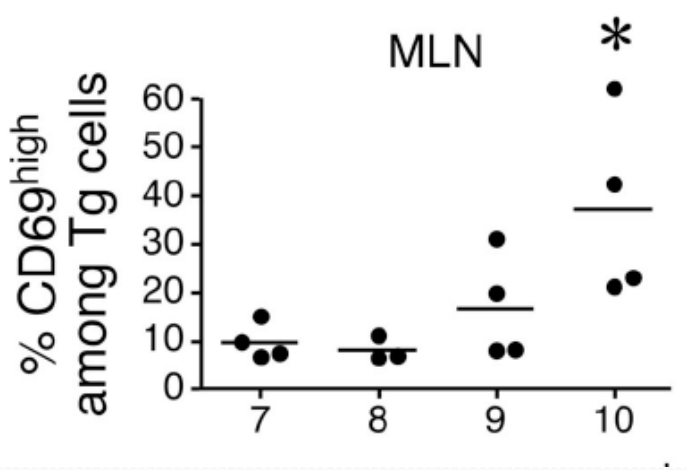
No increase in virus-specific T cell numbers until day 10.
T cells double every 18h.

Davenport *et al*, *Journal of Virology* 78, p10096 (2004)

Delayed & slow T cell growth in in tuberculosis.



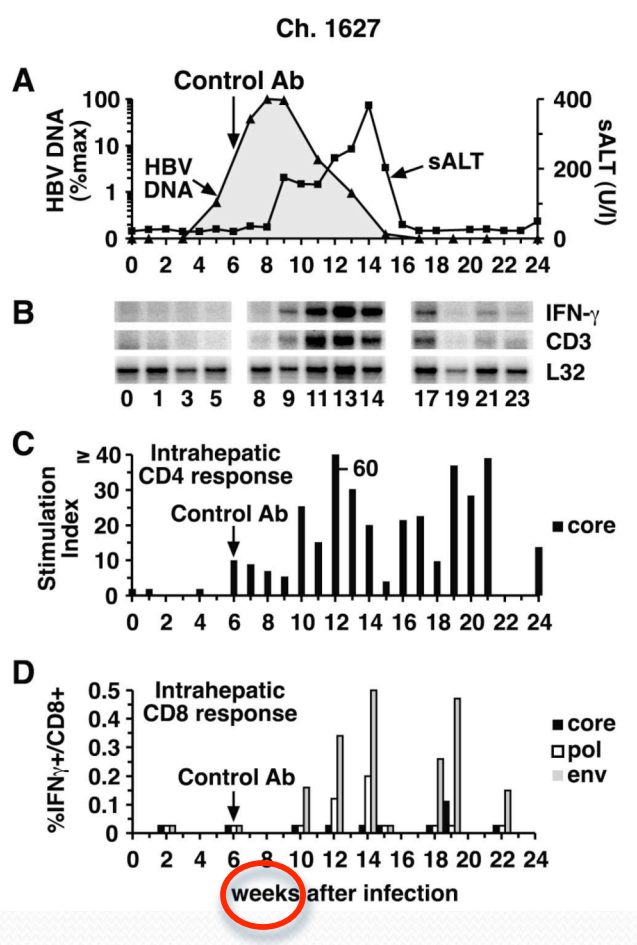
Wolf *et al*, JEM 2008



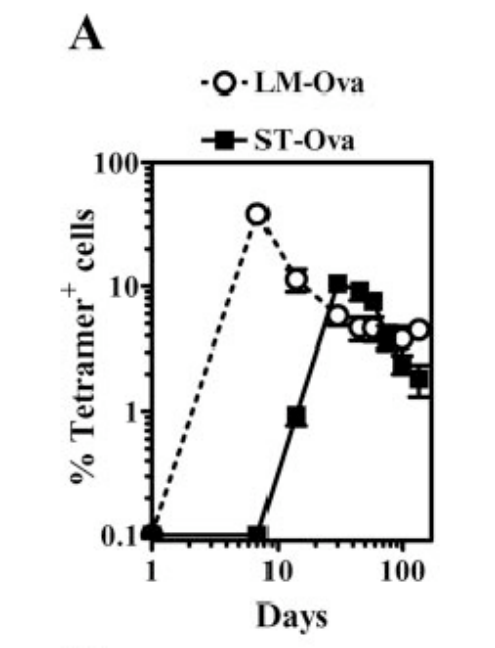
Reiley *et al*, PNAS 2008

- Delayed T cell activation in TB / BCG.

Delay in other infections



HBV (chimpanzee): Thimme, JVI 2003



Salmonella typhimurium: Luu *et al*, J Immunol 2006
LM = *Listeria monocytogenes*
ST = *Salmonella Typhimurium*

Compared to fast infections, T cell response in SHIV and TB infection is:

- Delayed in starting.
- Slow in growing.
- Fails to eliminate pathogen.

Slow infection = chronic infection

Slow infections.

- TB
- HIV / SIV
- HCV / HBV
- *Leishmania*
- *Toxoplasma*

Fast infections.

- Influenza
- Listeria
- Vaccinia

- LCMV

Questions

- How does slow pathogen growth affect immune dynamics?
- Is slow pathogen growth a major predictor of chronic infection?
- What vaccination strategies would work for slow growing pathogens?

Davenport, Trends in Immunology 2009.

Slow Pathogens and immune dynamics

- Why is initiation of T cell growth delayed?
- Why is T cell growth slow?
- Does growth affect differentiation?

Slow Pathogens and immune dynamics

- Why is initiation of T cell growth delayed?
- Why is T cell growth slow?
- Does growth affect differentiation?

Hypothesis:

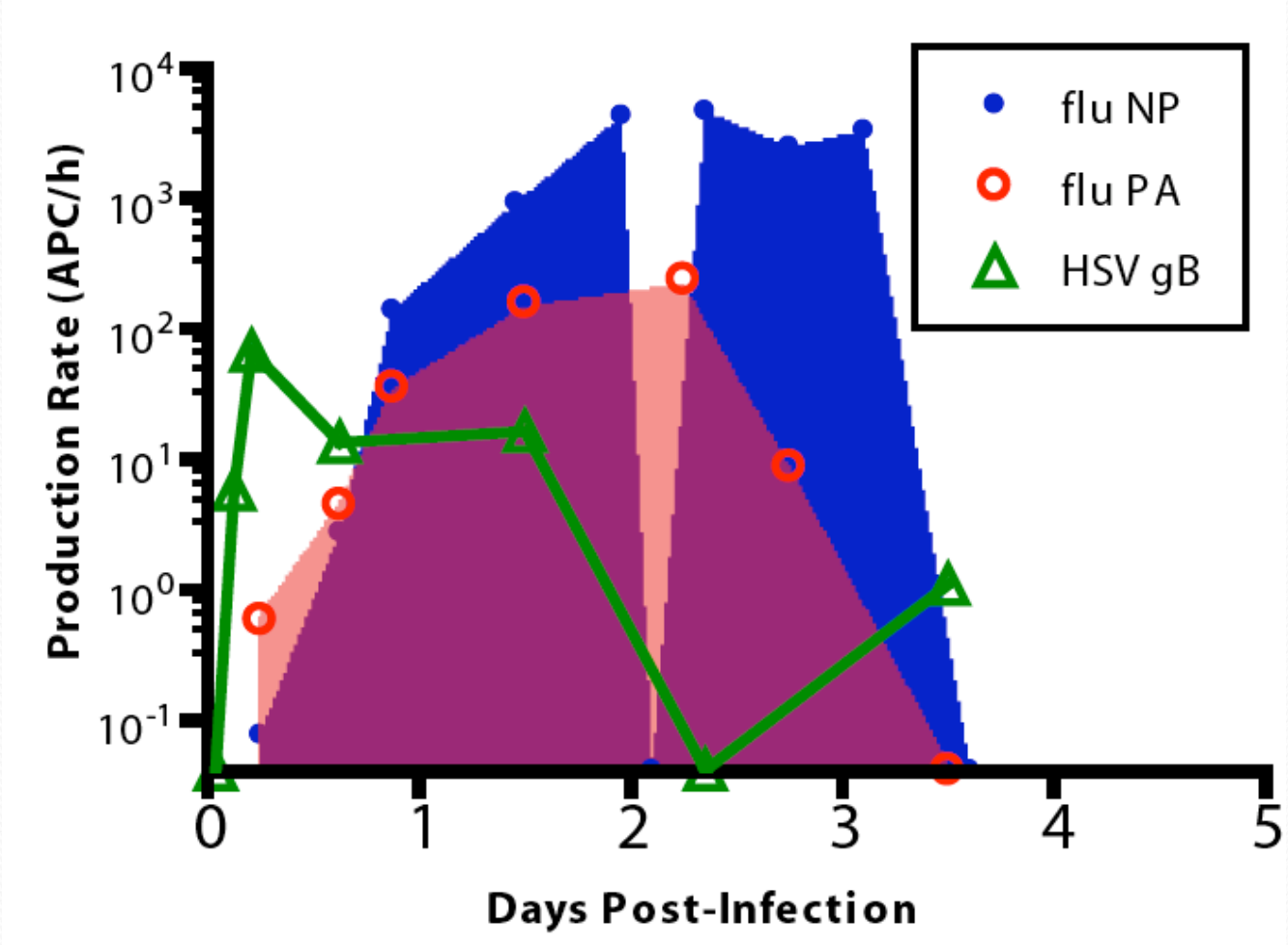
- The delay in initiation of T cell growth is due to a delay in infection reaching a 'threshold' level to drive antigen presentation. (Davenport, JVI 2004)

- Test: compare antigen presentation and viral kinetics in HSV and Flu infection in mice. (Lay *et al*, J Immunol 2009)

Antigen presentation dynamics.

- Use T cell hybridoma to measure antigen presentation.
- Influenza infection in mice (G. Belz).
- HSV infection (F. Carbone, S Mueller).

APC production



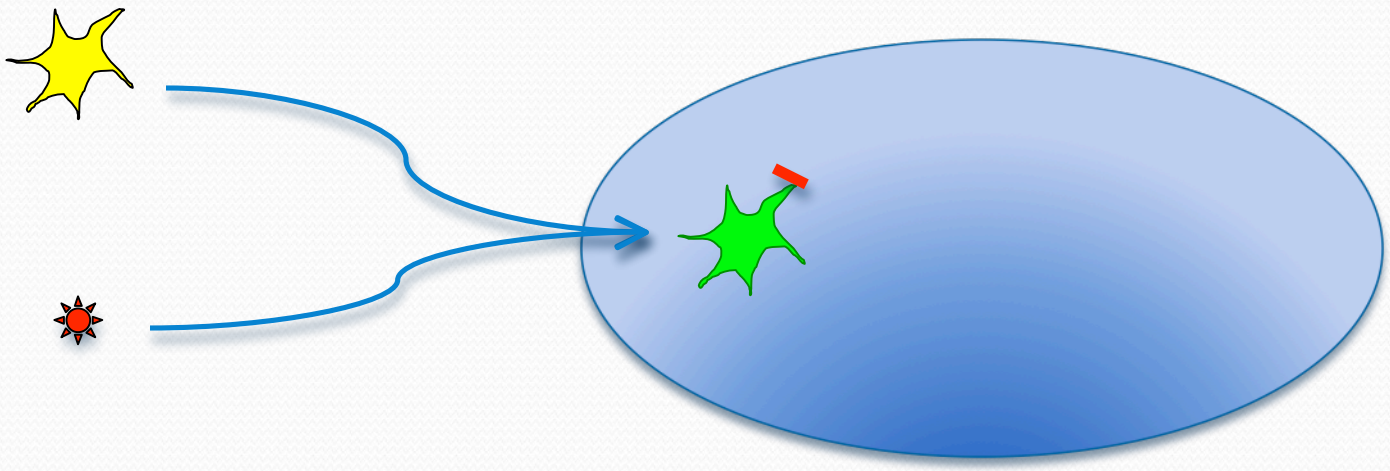
Lay *et al*, J Immunol 2009

APC production

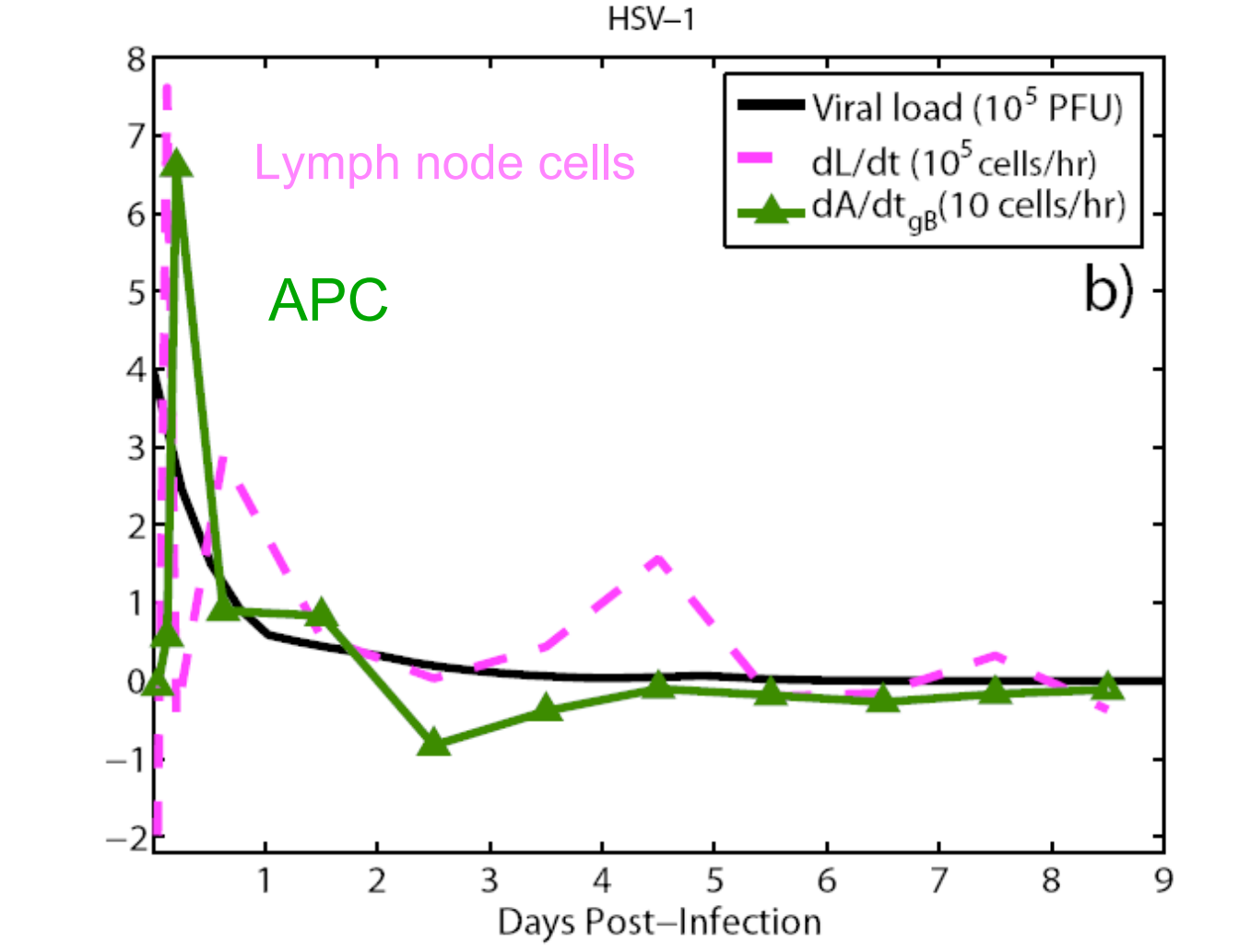
Requirements for antigen presentation:

1) Antigen. (viral load)

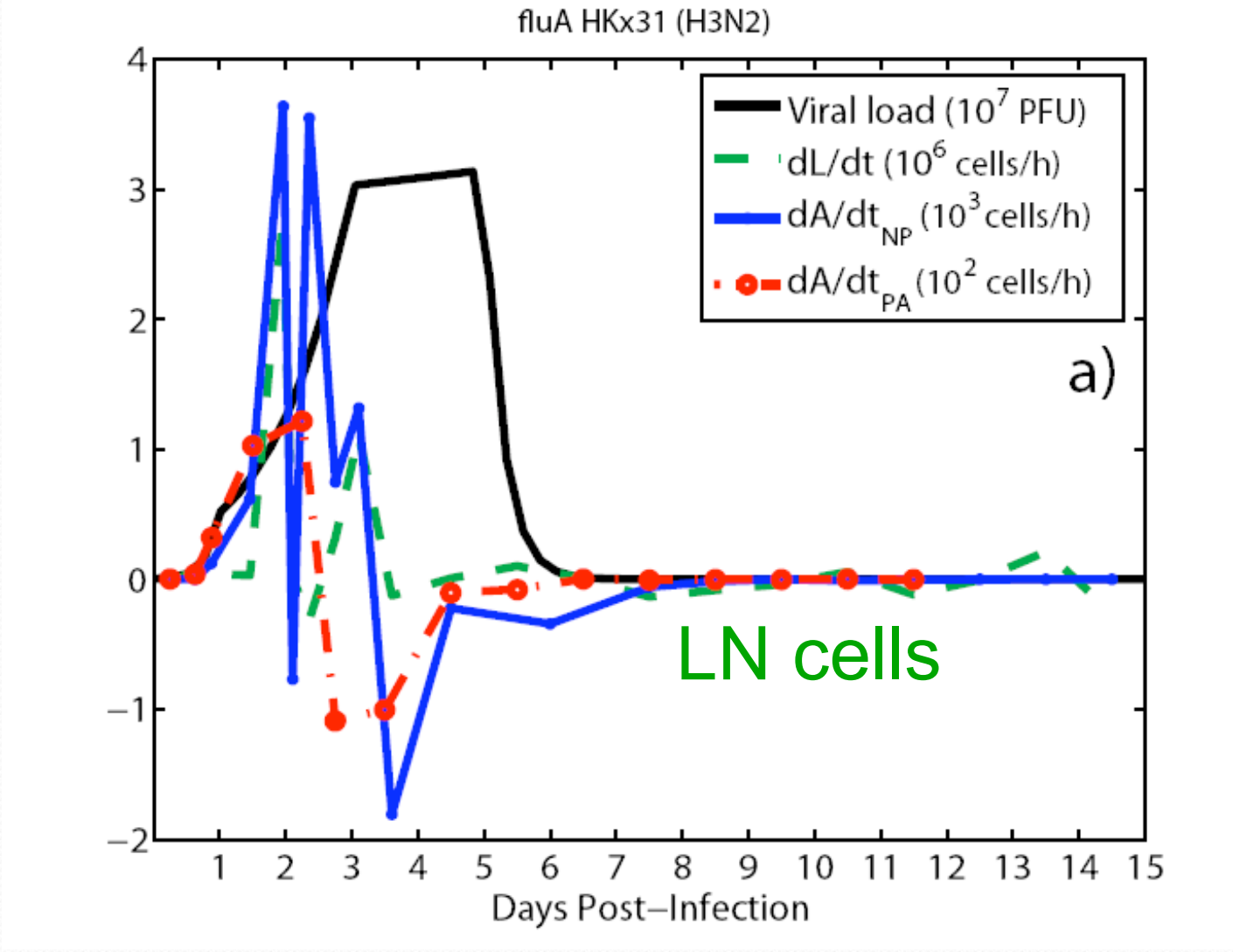
2) Inflammation / DC recruitment / DC activation. (lymph node swelling)



Early presentation in HSV.



Delayed presentation in Flu?



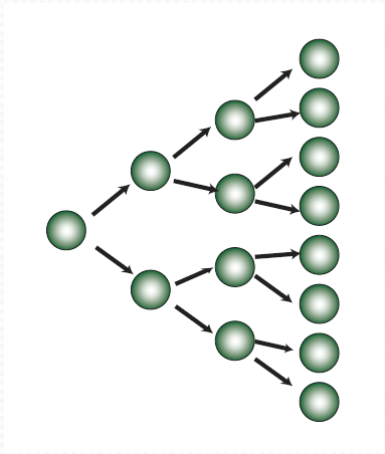
Conclusion:

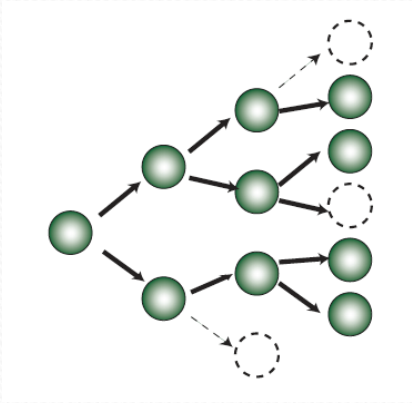
- Timing of antigen presentation coincides with timing of rapid lymph node cell recruitment.
- Delayed in flu due to delay in viral growth.
- ? Delayed in SHIV because viral growth even slower.
- Related to ***inflammation***.

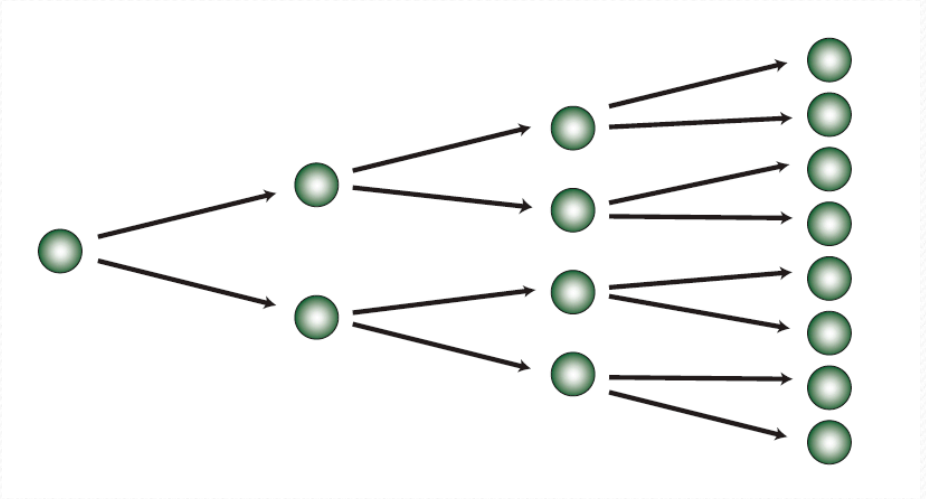
Slow Pathogens and immune dynamics

- Why is initiation of T cell growth delayed?
- Why is T cell growth slow?
- Does growth affect differentiation?

Slow T cell growth



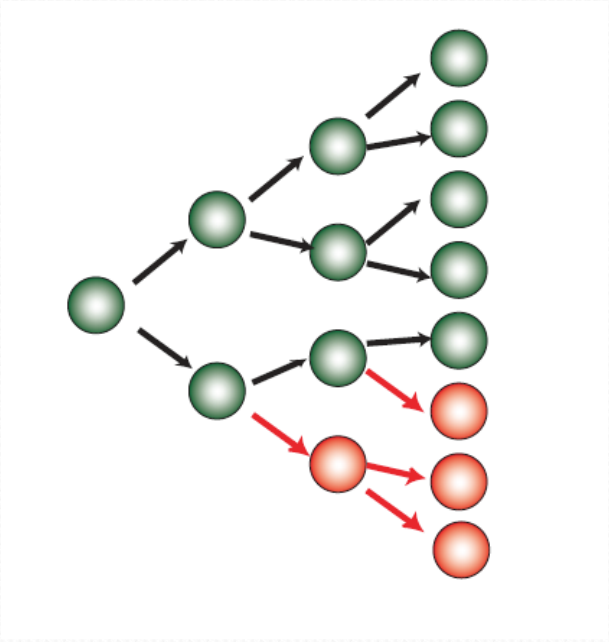




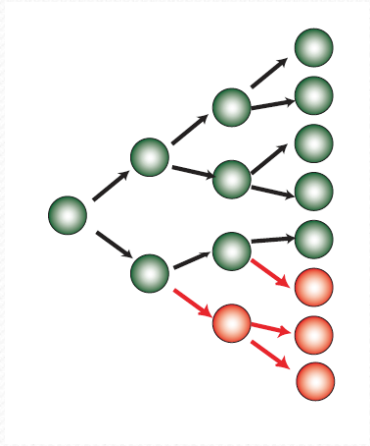
T cell division and differentiation

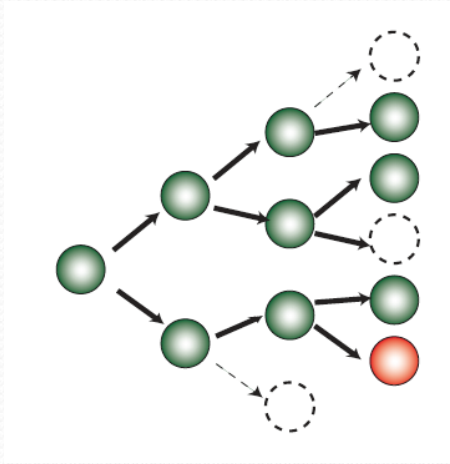
Division-linked differentiation

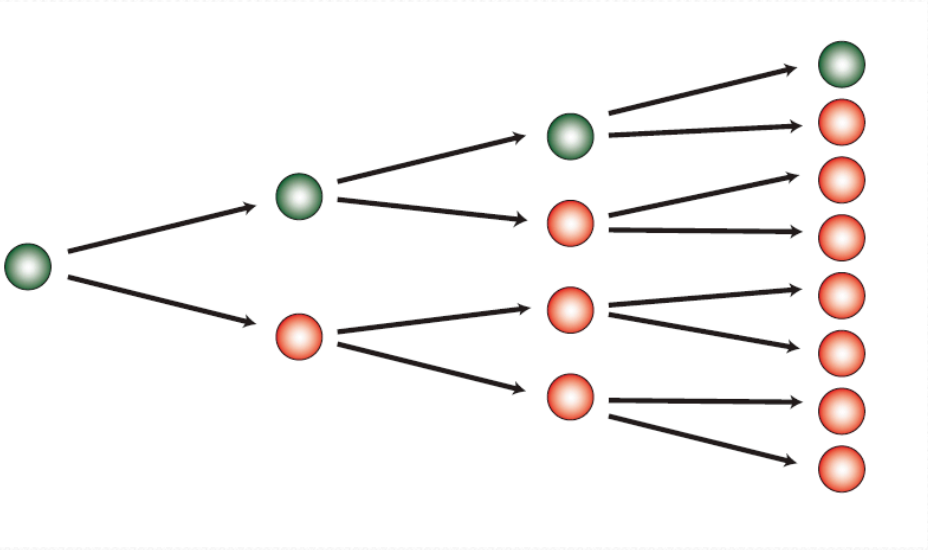
- T cells differentiate with division.
- Number of divisions predicts differentiation status.



Slow division and differentiation







Differentiation in acute infection

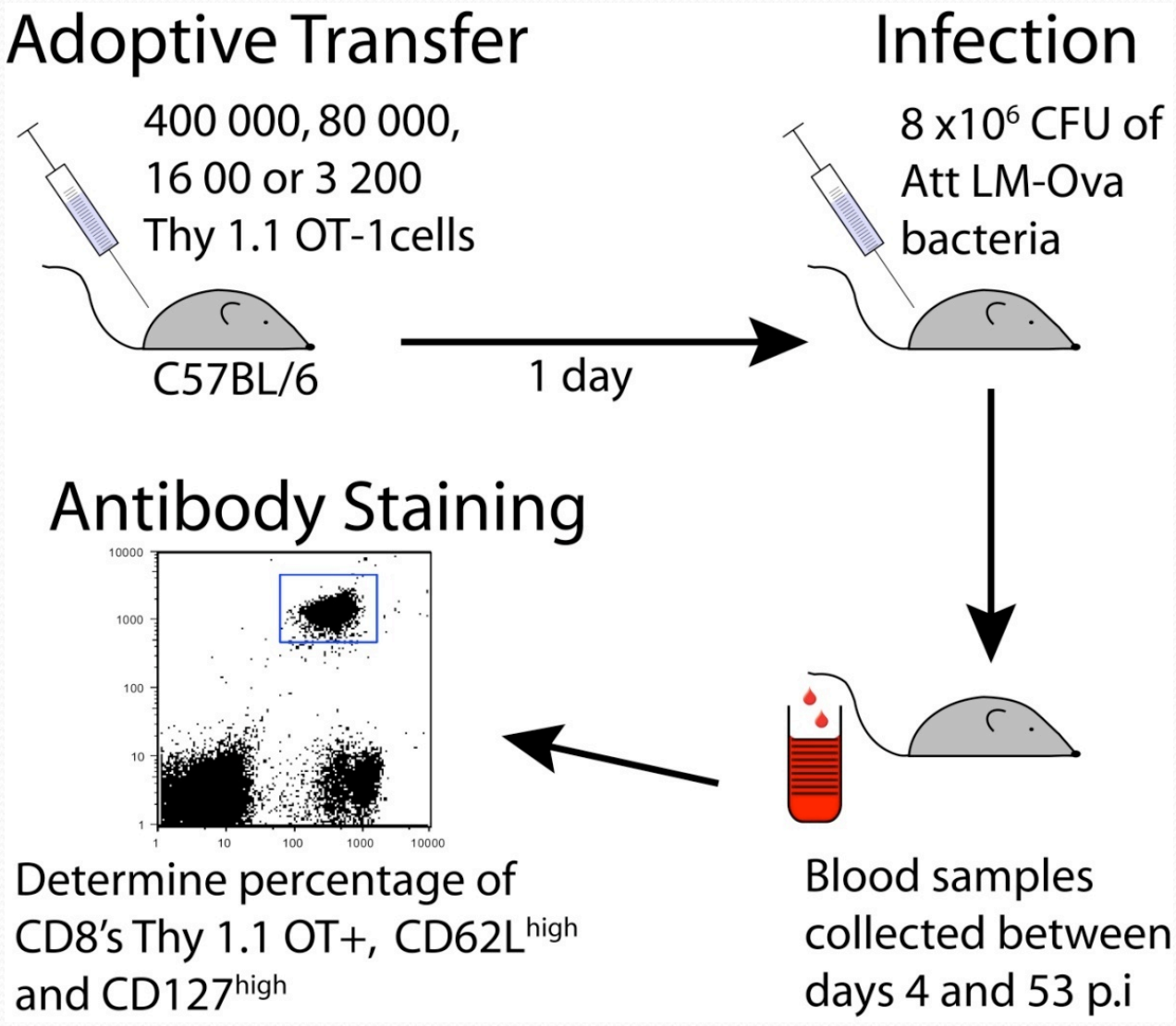
Differentiation and CD62L expression

- Adhesion molecule allowing entry into lymph nodes.
- High on naïve cells, down-regulated during acute response.
- Present on 'central memory' cells.

- Recently proposed that division-linked differentiation explains clonotype distribution of CD8 T cells in Influenza.

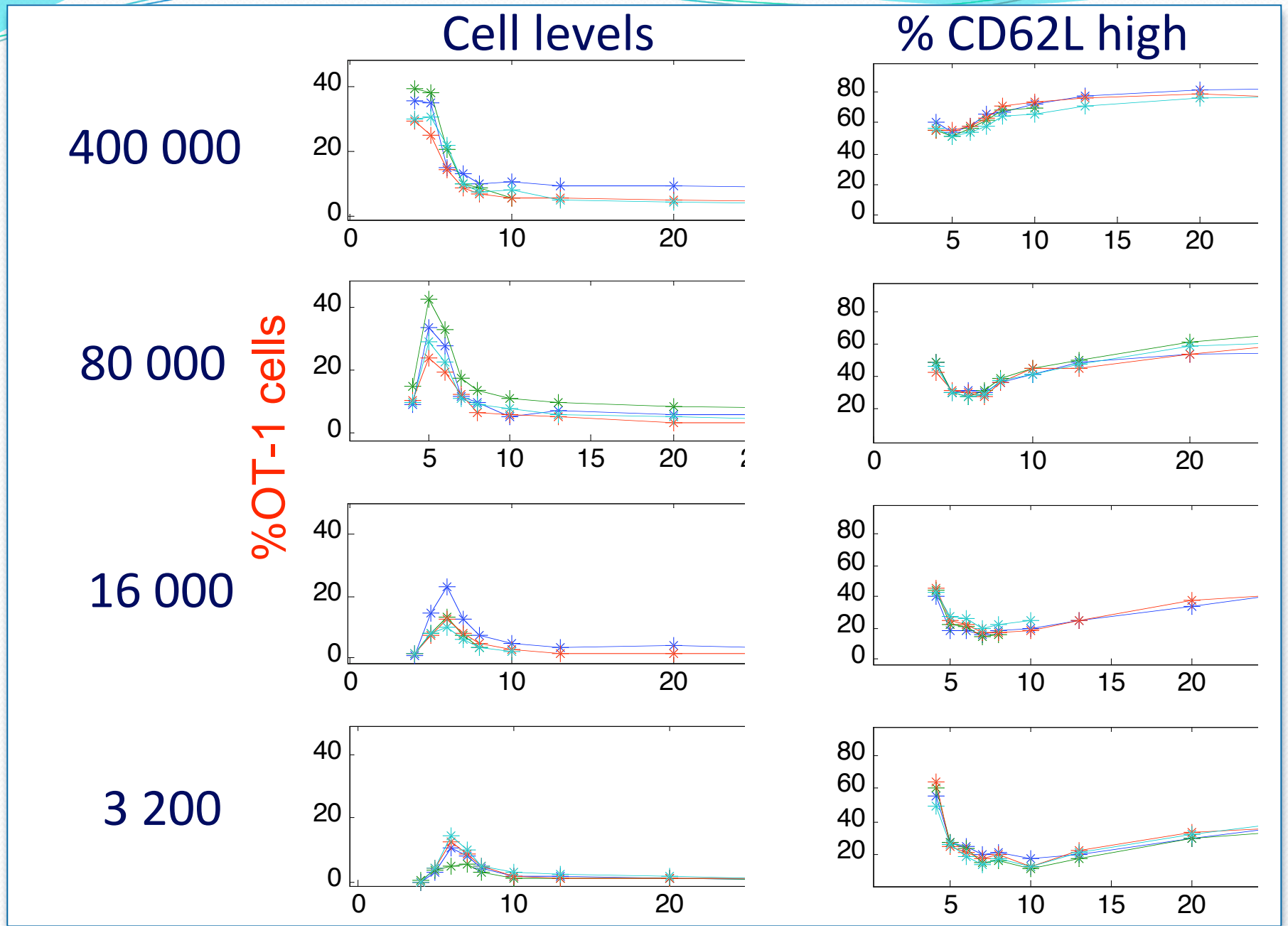
(Schlub *et al*, EJI 2009)

Differentiation in acute infection



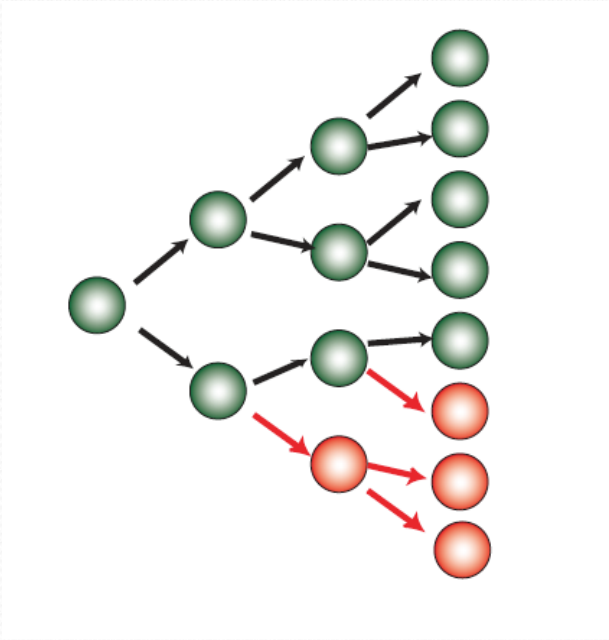
Harty and
Badovinac

Expression of CD62L



Division-linked differentiation *in vivo.*

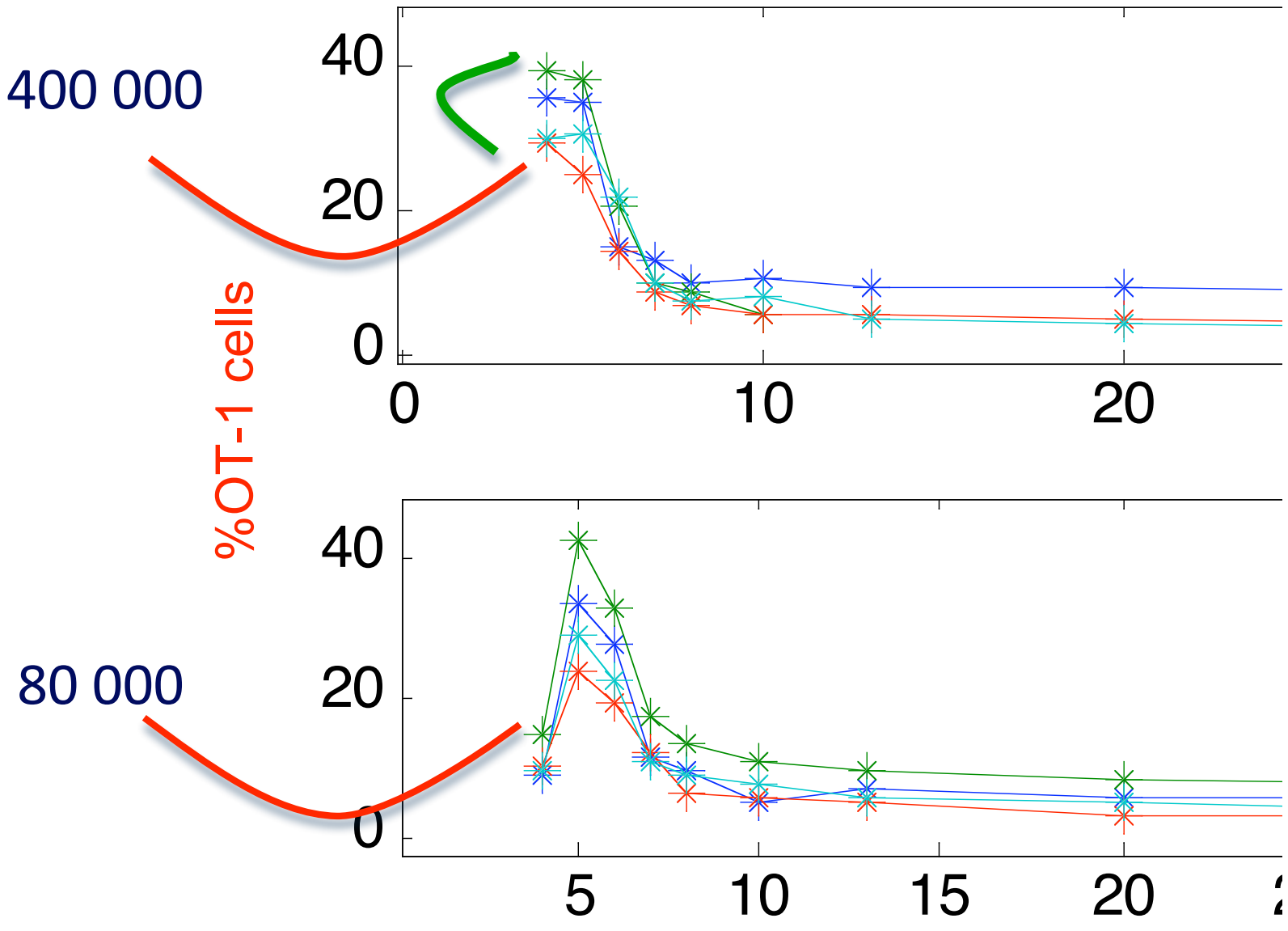
- If X% of cells lose CD62L every division, then after N divisions, the number of cells which remain CD62L high will be:



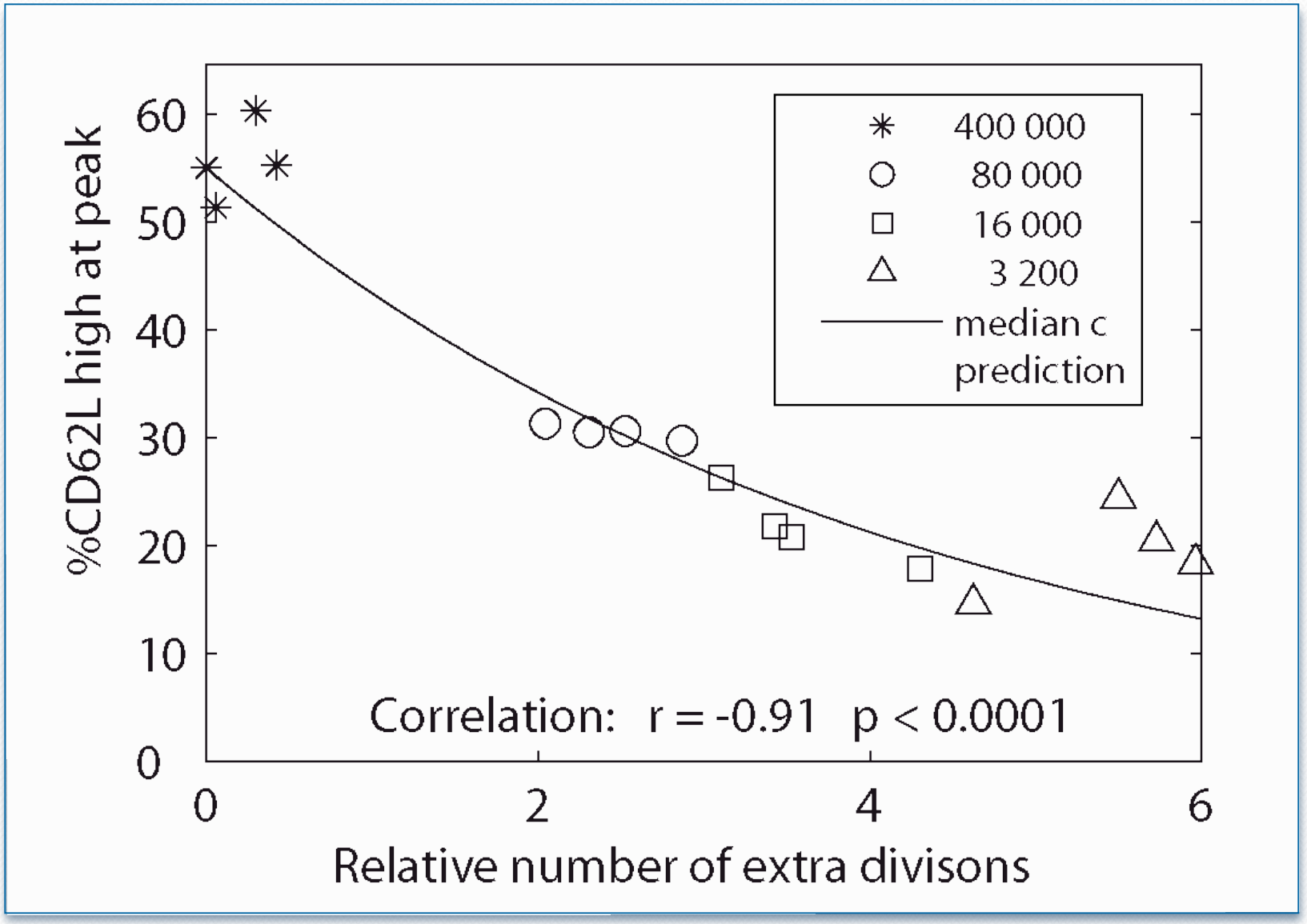
$$(100 - X)^N$$

Schlub et al, *Immunol Cell Biol* 2010

Relative number of divisions



Division predicts CD62L expression



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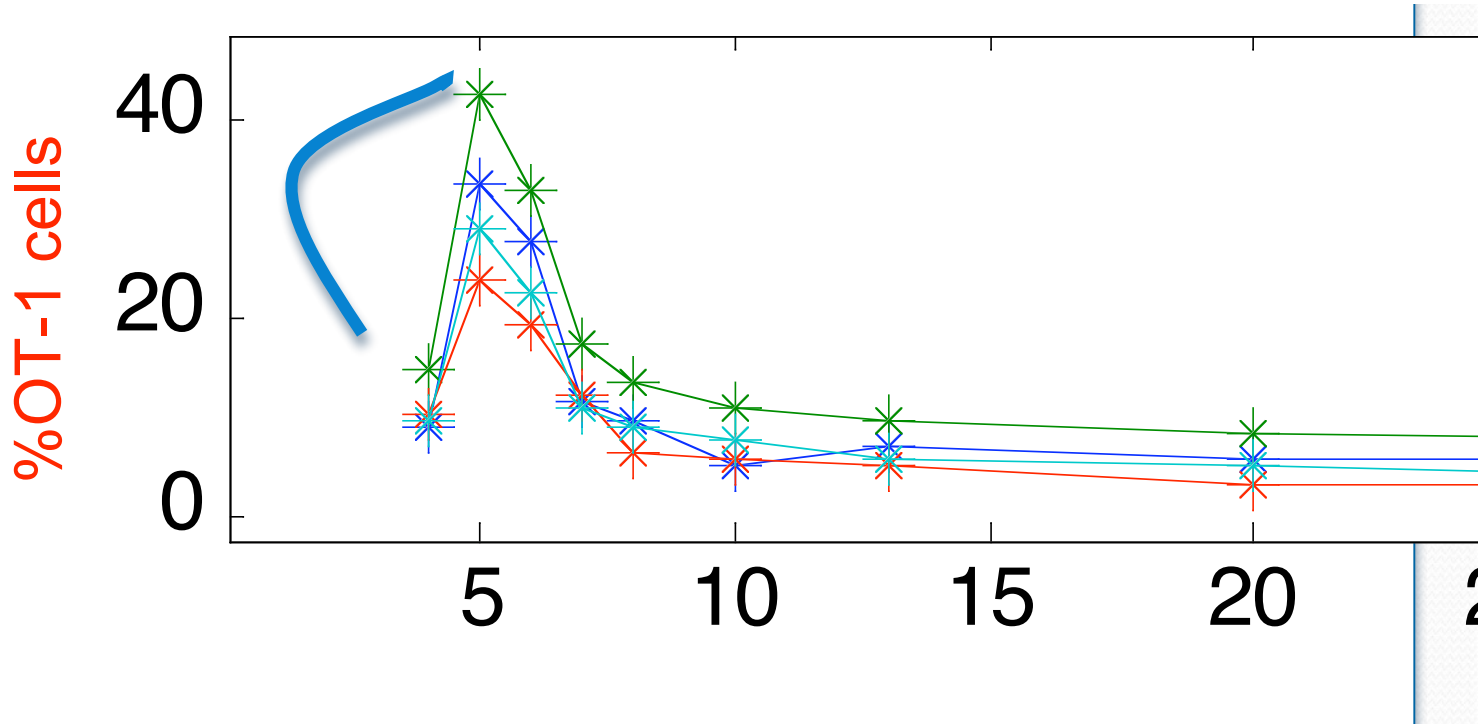
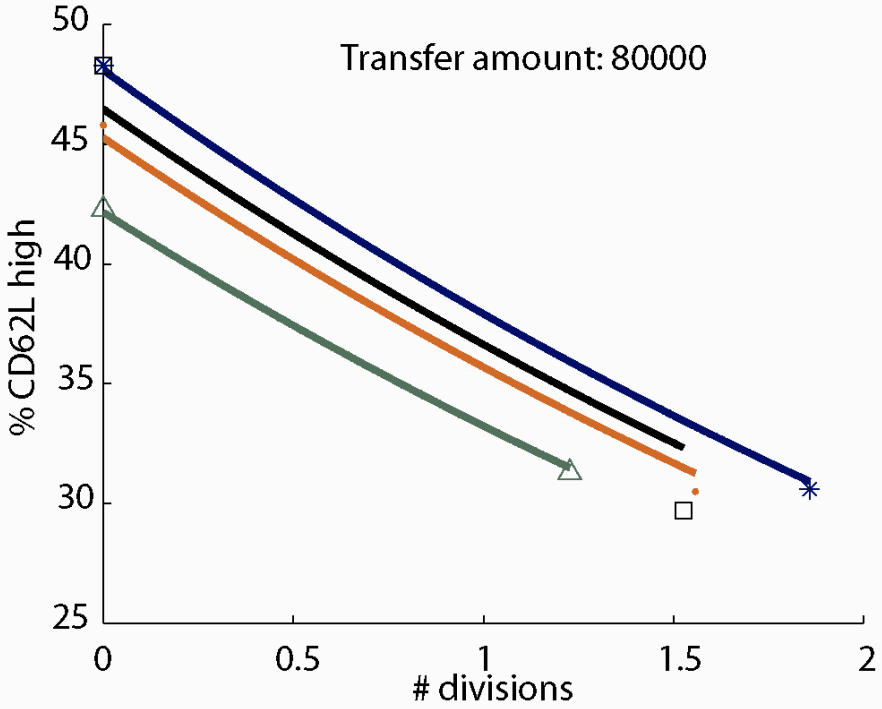
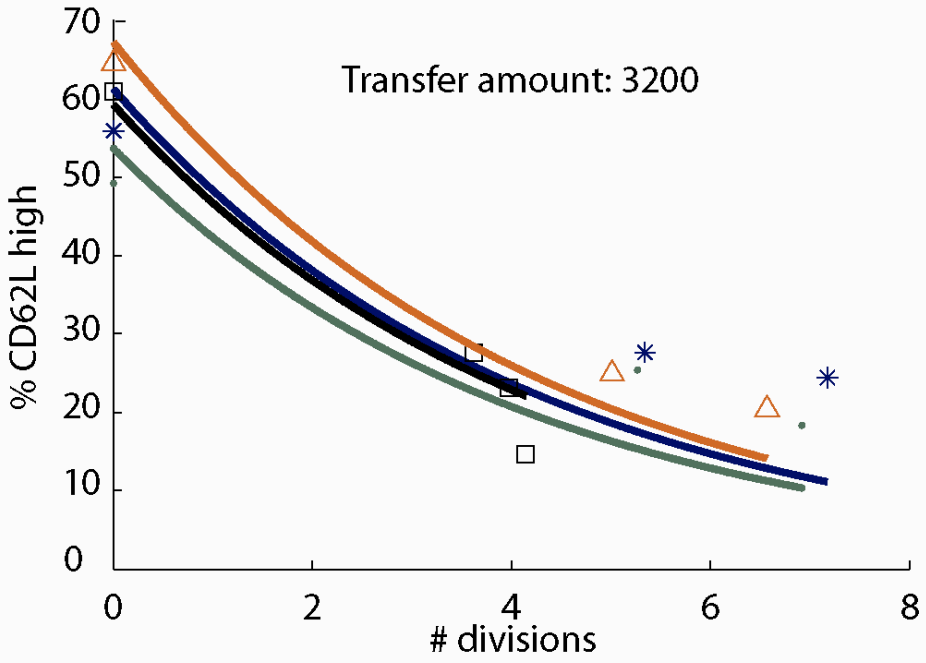
Expression of CD62L over time

80 000



Division and CD62L within mice





Conclusions

- For CD62L in LM infection, expression appears division-linked.
- 20% of cells lose CD62L per division.

Questions:

- ?how does slow growth occur?
- Does slow growth affect differentiation?
- Does altered differentiation lead to poor viral control and chronic infection?

Conclusions

- The race between infection and immunity is more complex than we thought.
- Slow growing pathogens elicit delayed T cell responses, slow growing responses, and tend to be chronic.

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Vaccine failure for chronic Infection: Are we simply running the wrong race?

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